Risk Management Plan (Summary)

Name of the medicinal product:	Nerlynx®
Active Substance:	Neratininb maleate
RMP Version number:	V.0.9 (dated 03 July 2018)
Marketing Authorisation Holder:	Voisin Consulting CH SARL 1015 Lausanne

Zul.-Nr. 67293

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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Nerlynx® is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Nerlynx® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

Voisin Consulting CH SARL is fully responsible for the accuracy and correctness of the content of the published summary RMP of Nerlynx®.

Summary of risk management plan for Nerlynx

This is a summary of the risk management plan (RMP) for Nerlynx. The RMP details important risks of Nerlyx, how these risks can be minimised, and how more information will be obtained about Nerlynx's risks and uncertainties (missing information).

Nerlynx's Information for Professionals (FI) and Information for Patients (PI) give essential information to healthcare professionals and patients on how Nerlyx should be used.

This summary of the RMP for Nerlynx should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the Swiss Public Assessment Report (SwissPAR).

Important new concerns or changes to the current ones will be included in updates of Nerlynx's RMP.

I. The medicine and what it is used for

Nerlynx is authorised as a single agent indicated for the extended adjuvant treatment of adult patients with early-stage hormone-receptor positive HER2-overexpressed/amplified breast cancer who are less than one year from the completion of prior adjuvant trastuzumab-based therapy and chemotherapy.

It contains neratinib maleate (INN) as the active substance and it is given orally.

Further information about the evaluation of Nerlynx's benefits can be found in Nerlyx's SwissPAR, including in its plain-language summary, available on the Swissmedic website, under the Human Medicines/Authorisations' webpage: https://www.swissmedic.ch/swissmedic/fr/home/humanarzneimittel/authorisations/swisspar.html

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Nerlynx, together with measures to minimise such risks and the proposed studies for learning more about Nerlynx's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PI and FI addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status (Category A – with medical prescription) — the way a medicine is supplied to the patient can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Nerlynx, these measures are supplemented *with additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks

Important risks of Nerlynx are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Nerlynx. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Important identified risks	• Gastrointestinal toxicity - Diarrhoea and stomatitis[a] • Hepatotoxicity
Important potential risks	• Cardiotoxicity - LVEF decreased • Pulmonary toxicity - Interstitial lung disease • Reproductive and developmental toxicity

Abbreviations: LVEF = left ventricular ejection fraction

a. Includes mucosal inflammation, stomatitis, aphthous stomatitis, mouth ulceration, and oral mucosal blistering

II.B Summary of important risks

The safety information in the FI is aligned to the reference medicinal product.

Important identified risks

Risk	What is known	Preventability
• Diarrhoea (diarrhoea)	• Approximately 94 in 100 patients may present with diarrhoea while taking Nerlynx. • Presence of chronic stomach and intestinal problems with diarrhoea as major symptom or a recent sudden episode of diarrhoea may increase the risk of having diarrhoea with Nerlynx. • Advanced age and taking certain concomitant drugs may increase the severity of diarrhoea.	• The risk of having diarrhoea can be managed by changing the dose of Nerlynx and through preventive treatment with anti-diarrhoeal medication started at the same time as Nerlynx.
• Swelling or irritation of the mucus membranes (stomatitis)	• Approximately 11 in 100 patients taking Nerlynx may experience swelling or irritation of the mucus membranes. • Malnutrition and poor oral health can increase the risk of stomatitis.	• Optimal oral hygiene including careful brushing with a soft bristle toothbrush, flossing, and non-medicated alcohol-free mouth rinses several times a day help prevent swelling or irritation of the mucus membranes.
• Liver damage (hepatotoxicity)	• Approximately 12 in 100 patients may have an increase in liver enzyme levels. • Nerlynx is mainly broken down in the liver, in large parts by a liver enzyme called CYP3A4. Concomitant use of drugs that block this specific liver enzyme will limit its ability to break down drugs. This will lead to an increase in the amount of Nerlynx in the body and potentially increase the risk of liver damage and other adverse reactions.	• Routine assessment of liver enzyme levels may detect potential cases of liver damage. • Periodic testing of liver function is recommended for patients with pre-existing liver disease. • Concomitant administration of drugs that block CYP3A4 should be avoided.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
• Damage to the lung (pulmonary toxicity – Interstitial lung disease)	• The risk of damage to the lung, in particular the tissue and space around the lungs, has been identified for drugs similar to Nerlynx. Clinical studies in humans did not indicate damage to the lung with Nerlynx.
• Damage to the heart (left ventricular ejection fraction)	• The risk of heart damage, in particular reduction in the volume of blood which is pumped out of the left ventricle of the heart during each beat (known as the left ventricular ejection fraction), has been identified for drugs similar to Nerlynx. Studies in animals and clinical studies in humans did not indicate damage to the heart with Nerlynx.
• Malformations in unborn foetuses (reproductive and developmental toxicity)	• There have been reports of malformations of the unborn foetuses and death in studies in animals. There is no experience with Nerlynx in pregnant women. Patients who are pregnant should not take Nerlynx. Patients who are fertile should avoid becoming pregnant while taking Nerlynx by using proper and effective contraception for a month after the last dose of Nerlynx.

Summary of risk minimisation measures by safety concerns

All medicines have an Information for Professionals (FI) which provides physicians, pharmacists, and other health care professionals with details on how to use the medicine, the risks, and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the Information for Patients (PI). The measures in these documents are known as routine risk minimisation measures.

The FI and the PI for Nerlynx can be found in the Nerlynx' SwissPAR.

This medicine has an additional risk minimisation measure including providing educational resources to patients and health care professionals.

Planned post-authorisation development plan

None.

Summary of changes to the risk management plan over time

Not applicable as this is the initial risk management plan.

- *Module SVII is not applicable but there are additional risk minimisation activities or additional pharmacovigilance activities:*

Important identified risk: Diarrhoea	
For diarrhoea in general, groups at risk include patients with significant chronic active inflammatory bowel disease or recent acute gastrointestinal disorder with diarrhoea as a major symptom (eg, Crohn's disease, ulcerative colitis, malabsorption, or grade ≥ 2 diarrhoea of any aetiology prior to treatment). Aggravating risk factors include concomitant medications and other predisposing conditions including advanced age. For diarrhoea during treatment with TKIs, a small number of emerging clinical investigations have found an association between drug steady-state concentrations and diarrhoea, suggesting that gene variants within metabolic pathways for TKIs could play a role in toxicity susceptibility (Bowen, 2013).	During the ExteNET study, where prophylaxis with loperamide was not mandatory, 95.5% of Nerlynx-treated adult patients with early-stage HER2-overexpressed/amplified breast cancer who have received prior adjuvant trastuzumab-based therapy experienced diarrhoea (all grades), versus 36.4% in the placebo arm. Serious diarrhoea was reported in 1.6% of patients in the Nerlynx arm vs 0.3% in the placebo arm. The proportion of patients with diarrhoea of grade 3 was 40.0% in the Nerlynx arm and 1.7% in the placebo arm. There was one non-serious case of grade 4 diarrhoea (0.1%) in the Nerlynx arm. Diarrhoea led to hospitalisation in 1.4% of Nerlynx-treated patients.
Risk minimisation measures	Routine risk minimisation measures Provide patients and health care professionals with educational material as additional resources to minimize diarrhoea.

Additional pharmacovigilance activities	PUMA-NER-6201. A study to characterise the incidence and severity of diarrhoea in patients with early-stage HER2+ breast cancer treated with neratinib and intensive loperamide prophylaxis, with or without anti-inflammatory treatment (budesonide), and with/without a bile acid sequestrant (colestipol). Study PUMA-NER-6202 is being planned to evaluate the efficacy of intensive loperamide prophylaxis with/without a bile acid sequestrant on incidence and severity of diarrhoea. An observational Study PUMA-NER-7201 is being planned to characterise the incidence rates and duration of diarrhoea. The study will also evaluate the use of antidiarrhoeal medication among new users of Nerlynx, assess the impact of Nerlynx therapy on quality of life, and further assess and characterized events of hepatotoxicity, cardiotoxicity (LVEF decreased), pulmonary toxicity (interstitial lung disease), reproductive and developmental toxicity. Study PUMA-NER-7202 is being planned to evaluate the availability, interpretability, and impact of Nerlynx Educational Materials

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no post-authorisation safety study category 1 or 2 or efficacy studies planned.

II.C.2 Other studies in post-authorisation development plan

Study PUMA-NER-6201 is being conducted to further evaluate the efficacy of intensive prophylactic treatment of diarrhoea.

Study PUMA-NER-6202 is being planned to evaluate the efficacy of intensive loperamide prophylaxis with/without a bile acid sequestrant on incidence and severity of diarrhoea.

An observational Study PUMA-NER-7201 is being planned to characterise the incidence rates and duration of diarrhoea. The study will also evaluate the use of antidiarrhoeal medication among new users of Nerlynx, to assess the impact of Nerlynx therapy on quality of life, and to further assess and characterized events of hepatotoxicity, cardiotoxicity (LVEF decreased), pulmonary toxicity (interstitial lung disease), reproductive and developmental toxicity.

Study PUMA-NER-7202 is being planned to evaluate the availability, interpretability, and impact of Nerlynx Educational Materials.